UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **September 7, 2016**

SUBJECT: Science Review of Pre-application Rationales in lieu of Guideline Studies in Support of the Registration of Natamycin as a new TGAI

Type of Data Review:	Human Health & Non-target Organism
Decision Number:	518809
DP Number:	435126
EPA File Symbol Number:	92311PA1
Chemical Class:	Biochemical
PC Code:	051102
Tolerance Exemptions:	40 CFR § 180.1315
MRID Nos.:	49957201

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THROUGH : Russell Jones, Senior Scientist
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TO: Cheryl Greene, Regulatory Action Leader
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ACTION REQUESTED

Ceradis B.V. has submitted pre-application rationales in lieu of guideline studies for some human health and non-target organism data requirements. Natamycin is a naturally occurring compound produced by several *Streptomyces* species that have been isolated from soils worldwide, including in the U.S. It is intended for formulation into end-use seed-treatment products to inhibit the germination of the spores of plant pathogenic fungi during the earliest stages of plant growth.

This review is a response to the registrant's rationales in lieu of guideline studies.

RECOMMENDATIONS AND CONCLUSIONS

1. All submitted rationales are **ACCEPTABLE**, given that the following point is implemented by the registrant:
   MRID 49957201

    a. All future product labels should ensure that proper personal protective equipment is required for all who handle the product, including gloves.

RATIONALE SUMMARIES

1. OCSPP 870.3250 90-day Dermal Toxicity: A request was evaluated to address the requirement for a 90-day dermal toxicity test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a 90-day dermal toxicity laboratory test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected into soil)
    d. Low potential exposure to applicators and growers
    e. Rapid UV degradation in the soil
    f. Long history of safe use for humans (used in ointments)
    g. Sufficient personal protective equipment (PPE)

CLASSIFICATION: ACCEPTABLE

2. OCSPP 870.3100 90-day Oral Toxicity: A request was evaluated to address the requirement for a 90-day oral toxicity test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a 90-day oral toxicity laboratory test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected into soil)
    d. Lack of oral exposure to applicators and growers
    e. Rapid UV degradation in the soil
    f. Long history of safe use for humans (food additive)
    g. Even if swallowed, would breakdown quickly in low pH of stomach
    h. Natamycin's low water solubility, low absorption into GI tract of mammals, and rapid fecal excretion indicates minimal chance of human/animal toxicity

i. Absence of ergosterol in cell membranes of mammalian cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)
j. Sufficient personal protective equipment (PPE)

CLASSIFICATION: ACCEPTABLE

3. OCSPP 870.3465 90-day Inhalation Toxicity: A request was evaluated to address the requirement for a 90-day inhalation toxicity test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a 90-day inhalation toxicity laboratory test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected into soil)
    d. Lack of inhalation exposure to applicators and growers
    e. Rapid UV degradation in the soil
    f. Long history of safe use for humans (food additive and topical fungal treatment)
    g. Natamycin's low water solubility, low absorption into GI tract of mammals, and rapid fecal excretion indicates minimal chance of human/animal toxicity
    h. Absence of ergosterol in cell membranes of mammalian cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)
    i. Sufficient personal protective equipment (PPE)

CLASSIFICATION: ACCEPTABLE

4. OCSPP 870.3700 Prenatal Development Toxicity: A request was evaluated to address the requirement for a prenatal development toxicity test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a prenatal development toxicity laboratory test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected into soil)
    d. Lack of exposure to applicators and growers
    e. Rapid UV degradation in the soil
    f. Long history of safe use for humans (food additive and topical fungal treatment)
    g. Natamycin's low water solubility, low absorption into GI tract of mammals, and rapid fecal excretion indicates minimal chance of human/animal toxicity
    h. Absence of ergosterol in cell membranes of mammalian cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)
    i. Sufficient personal protective equipment (PPE)

CLASSIFICATION: ACCEPTABLE

5. OCSPP 870.5100 Bacterial Reverse Mutation Test: A request was evaluated to address the requirement for a bacterial reverse mutation test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a bacterial reverse mutation test is not necessary:
    a. Lack of mutagenicity in previously conducted GLP-compliant bacterial reverse mutation tests in Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, with and without metabolic activation
    b. Seed treatment use
    c. Very low application rates
    d. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected into soil)
    e. Lack of exposure to applicators and growers
    f. Rapid UV degradation in the soil
    g. Long history of safe use for humans (food additive and topical fungal treatment)
    h. Natamycin's low water solubility, low absorption into GI tract of mammals, and rapid fecal excretion indicates minimal chance of human/animal toxicity
    i. Absence of ergosterol in cell membranes of mammalian cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)
    j. Sufficient personal protective equipment (PPE)

CLASSIFICATION: ACCEPTABLE

6. OCSPP 870.5300/5375 In-vitro Mammalian Cell Assay: A request was evaluated to address the requirement for an in-vitro mammalian cell assay for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that an in-vitro mammalian cell assay is not necessary:
    a. Lack of mutagenicity in previously conducted GLP-compliant mouse lymphoma mutation assay at the TK locus (with and without metabolic activation) and a chromosomal aberration assay with Chinese hamster ovary (CHO) cells in vitro
    b. Seed treatment use
    c. Very low application rates
    d. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected into soil)
    e. Lack of exposure to applicators and growers
    f. Rapid UV degradation in the soil
    g. Long history of safe use for humans (food additive and topical fungal treatment)
    h. Natamycin's low water solubility, low absorption into GI tract of mammals, and rapid fecal excretion indicates minimal chance of human/animal toxicity
    i. Absence of ergosterol in cell membranes of mammalian cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)
    j. Sufficient personal protective equipment (PPE)

CLASSIFICATION: ACCEPTABLE

7. OCSPP 850.1010 Aquatic Invertebrate Toxicity, Freshwater: A request was evaluated to address the requirement for an aquatic invertebrate toxicity test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that an aquatic invertebrate toxicity test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected and buried into soil)
    d. No applications to water or topical soil/vegetation, so no expected exposure to aquatic invertebrates
    e. Rapid UV degradation in the soil
    f. Even if minimal exposure occurs, the potential risk of toxicity is extremely low due to the absence of ergosterol in cell membranes of aquatic invertebrate cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)

CLASSIFICATION: ACCEPTABLE

8. OCSPP 850.1075 Fish Acute Toxicity, Freshwater: A request was evaluated to address the requirement for a fish toxicity test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a fish toxicity test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected and buried into soil)
    d. No applications to water or topical soil/vegetation, so no expected exposure to freshwater fish
    e. Rapid UV degradation in the soil
    f. Even if minimal exposure occurs, the potential risk of toxicity is extremely low due to the absence of ergosterol in cell membranes of fish cells (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)

CLASSIFICATION: ACCEPTABLE

9. OCSPP 850.4350 Nontarget Insect Testing: A request was evaluated to address the requirement for a nontarget insect test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a nontarget insect test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected and buried into soil)
    d. Rapid UV degradation in the soil

e. Even if minimal exposure occurs, the potential risk of toxicity is extremely low due to the absence of ergosterol in cell membranes of insects (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)

CLASSIFICATION: ACCEPTABLE

10. OCSPP 850.4100 Terrestrial Plant Toxicity: Seedling Emergence: A request was evaluated to address the requirement for a seedling emergence test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a seedling emergence insect test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure to nontarget plants (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected and buried into soil)
    d. Rapid UV degradation in the soil
    e. Even if minimal exposure occurs, the potential risk of toxicity is extremely low due to the absence of ergosterol in cell membranes of plants (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)

CLASSIFICATION: ACCEPTABLE

11. OCSPP 850.4100 Terrestrial Plant Toxicity: Vegetative Vigor: A request was evaluated to address the requirement for a vegetative vigor test for a new TGAI (Natamycin) as a fungicide. This request is based on the following points which demonstrate that a vegetative vigor insect test is not necessary:
    a. Seed treatment use
    b. Very low application rates
    c. Methods of application greatly reduces risk of exposure to nontarget plants (automatically applied to seed indoors in a closed-treatment system; mechanically packaged; seeds loaded into mechanical seed drills and injected and buried into soil)
    d. Rapid UV degradation in the soil
    e. Even if minimal exposure occurs, the potential risk of toxicity is extremely low due to the absence of ergosterol in cell membranes of plants (natamycin binds to ergosterol as mode of action and ergosterol only found in fungal cell membranes)

CLASSIFICATION: ACCEPTABLE